

Evaluation of the Free Triiodothyronine/Free Thyroxine ratio and Euthyroid Sick Syndrome in patients with COVID-19: A cross-sectional study

Euthyroid Sick Syndrome and COVID-19

Durmuş Ayan¹, Tevfik Balcı¹, Sercan Ünal², Haydar Ulucan³, Cevdet Türkyürek¹, Ergül Bayram¹¹ Department of Medical Biochemistry, Niğde Research and Training Hospital, Niğde² Department of Internal Medicine, Niğde Research and Training Hospital, Niğde³ Department of Radiology, Health Sciences University Samsun Research and Training Hospital, Samsun, Turkey

Abstract

Aim: In our study, we aimed to evaluate the prevalence of euthyroid sick syndrome among patients with COVID-19, and the relationship between the possible change in free-triiodothyronine/free-thyroxine (FT3/FT4) ratio and the biochemical parameters used during the follow-up of COVID-19.

Material and Methods: A total of 114 sequential patients between 18-65 years of age, who were treated in the internal medicine service allocated to patients with COVID-19, were included in the study. FT3, FT4, thyroid-stimulating hormone (TSH), thyroid peroxidase antibodies, and thyroglobulin antibodies antibody levels were analyzed. FT3/FT4 ratio was calculated.

Results: According to the results, only isolated low FT3 levels were found in 39.5% (45/114) of the patients, while 25.4% (29/114) had both low TSH and FT3 levels, 31.6% (36/114) had autoimmune thyroid disease, and 3.5% (4/114) had normal results in the thyroid function tests. The FT3/FT4 ratio was also determined to be low in all groups. However, no significant correlation was found between the low FT3/FT4 ratio and the parameters used in monitoring COVID-19.

Discussion: We believe that studies with a wider scope of participants are needed for testing the reduction in FT3/FT4 ratio with other biochemical parameters in patients with COVID-19 and without known thyroid disease.

Keywords

SARS-CoV-2, Thyroid Disease, Thyroid Hormones, ESS, COVID-19

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Corresponding Author: Durmuş Ayan, Aşağıkayabaşı mahallesi, Hastaneler caddesi, Niğde Research and Training Hospital, Department of Medical Biochemistry, 5100, Niğde, Turkey.

E-mail: durmusayan@hotmail.com P: +90 553 633 81 85

Corresponding Author ORCID ID: <https://orcid.org/0000-0003-2615-8474>

Introduction

The novel type of coronavirus, which is known as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), is responsible for the Coronavirus 19 (COVID-19) global pandemic that started in late 2019. COVID-19 can range from a very mild or asymptomatic clinical picture to critical illness and death [1]. The data obtained indicated that the severity of COVID-19 was associated with the interleukin (IL)-2, IL-7, IL-10, tumor necrosis factor (TNF). The fatal COVID-19 has been characterized as a cytokine release syndrome (CRS) induced by the cytokine storm with a high mortality rate [2].

One of the systems that may be affected by COVID-19 is the thyroid gland. Specifically, thyroid disorders associated with COVID-19 include thyrotoxicosis, hypothyroidism, and non-thyroidal illness syndrome [3]. Changes in thyroid function parameters, commonly referred to as “non-thyroidal illness syndrome” (or euthyroid sick syndrome (ESS) or low triiodothyronine (T3) syndrome), can be detected in many serious clinical acute and chronic conditions. The most typical change is a decrease in serum T3 level. This may or may not be accompanied by a slight decrease in the level of thyroid-stimulating hormone (TSH) [4]. As the severity and duration of non-thyroidal illness syndrome (NTIS) increases, levels of total tetraiodothyronine (T4) will also increase. The magnitude of TSH and thyroid hormone changes is proportional to the severity of the underlying condition of NTIS, and the changes usually regress once the cause of the disease is eliminated [4]. NTIS has been considered as an adaptation mechanism in reduced tissue metabolism in order to conserve energy during systemic diseases. The conversion of the T4 prohormone to the biologically active hormone T3 is catalyzed by type 1 (DIO1) and type 2 (DIO2) deiodinases [5]. In contrast, type 3 deiodinase (DIO3) catalyzes the inactivation of both T4 and T3. DIO3 creates two biologically inactive forms, by regulating the conversion of T4 to reverse T3 and the conversion of T3 to 3,3-T2.

Decreased conversion of T4 to T3 and increased activity of DIO3 are typically observed in NTIS. NTIS is common in patients treated in intensive care units (ICU) for sepsis, trauma, acute myocardial infarction, and patients with pneumonia [6, 7].

The cytokine storm associated with SARS-CoV-2 contributes to non-thyroid illness syndrome with three different mechanisms in patients with COVID-19. First of all, it causes negative feedback on TRH and NTIS secretion as it increases the conversion of T4 to T3 by decreasing the secretion and release of the thyroid releasing hormone (TRH) and NTSI and increasing the DIO2 activity. Secondly, it is thought to reduce the expression of DIO1 and DIO2 by reducing iodine uptake, T3 secretion, and mRNA expressions of thyroid-specific genes in the thyroid gland. Therefore, the conversion of T4 to T3 is decreased. It is stated that the conversion of T3 to reverse T3 will increase as DIO3 activity and expression increase. Thirdly, cytokine storm associated with SARS-CoV-2 leads to a decrease in the secretion of proteins carrying thyroid hormones (thyroxine-binding globulin, thyroxine-binding prealbumin or transthyretin, albumin, and lipoproteins) in the liver [6].

Recently, the fT3/ fT4 ratio has been used to obtain information about the status of the enzyme activity of 5-deiodinase [8-10].

In our study, we aimed to determine the frequency of ESS in patients who were hospitalized after the diagnosis of COVID-19 and to compare the possible change in the fT3/fT4 ratio with the biochemical parameters used in the follow-up of COVID-19.

Material and Methods

Study Design, Participants, and Collection of Blood Samples

This study is a prospective, analytical and cross-sectional study. The study was approved by the Non-Interventional Clinical Research Ethics Committee of Niğde Ömer Halisdemir University (No.2021/51). A total of 144 patients between 18 and 65 years of age, who were confirmed to have COVID-19 with the PCR (polymerase chain reaction) test in the laboratory and were treated in the internal medicine clinic allocated to the patients with COVID-19 at Niğde Training and Research Hospital, were sequentially and randomly included in our study. Blood samples were obtained from these patients in the mornings on an empty stomach. Serums were obtained after the blood samples were centrifuged at 4000 rpm for 10 minutes. In addition to the routine tests performed during the follow-up of COVID-19 (CRP, troponin T, procalcitonin, D-dimer, leukocyte, ferritin), thyroid peroxidase antibodies (TPOAb), thyroglobulin antibodies (TgAb), TSH, fT3, and fT4 levels were determined in the sera obtained. The ratio of fT3/fT4 was calculated according to the results of the analysis on fT3 and fT4 tests. After the analyses, patients were classified as patients with autoimmune thyroid disease (Group I), patients with ESS and only isolated low fT3 levels (Group II), and patients with both isolated low fT3 and low TSH levels (Group III). Patients with normal thyroid function tests (n= 4) were not classified in a group, as their quantity was statistically small. In addition, the findings of the patients in the lung tomography were evaluated together with the test results. Patients with a history of thyroid disease other than autoimmune thyroid disease, who had undergone thyroid surgery, who had used medication for thyroid, who had a known history of coronary heart disease, who had liver disease or failure, who had known chronic inflammatory disease (FMF, rheumatoid arthritis, tuberculosis, etc.), who received chemotherapy and radiotherapy, and who had pituitary and hypothalamic diseases within the last 6 months, were excluded from the study.

Measurement of Parameters

TPOAb, TgAb, TSH, fT3, fT4, and the levels of troponin T, procalcitonin, and ferritin from the tests in the routine test panel were measured through the ECLIA (electrochemiluminescence assay) method on a Roche Cobas 8000 (Roche Diagnostics GmbH, Mannheim; Germany) hormone analyzer. CRP levels were measured using the immunoturbidimetry method on a Roche Cobas c701 (Roche Diagnostics GmbH, Mannheim; Germany) biochemistry analyzer, D-dimer levels were measured using the coagulometric method on ACL-TOP 700 (Instrumentation Laboratory) coagulation analyzer, and the leukocyte levels were measured using the fluorescence flow cytometry method on the Sysmex XN-1000 (Sysmex Corporation, Kobe, Japan) hematology analyzer. Normal reference ranges for thyroid function tests and thyroid antibodies were accepted as 0-34 U/ml for TPOAb, 0-115 U/ml for TgAb, 1.95-5.85 ng/L for fT3, 0.9-1.7 ng/dl for fT4, and 0.27-4.2 mIU/L for TSH.

Statistical analysis

The SPSS 15.0 software for Windows was used for statistical analysis. Descriptive statistics were presented as numbers and percentages for categorical variables, and as interquartile range (IQR) and median for the numerical variables. Normal distribution was determined by skewness, kurtosis, Kolmogorov-Smirnov (Lilliefors Significance Correction), Shapiro-Wilk tests, and examination of the distribution of histogram graphics. After the Kruskal-Wallis analysis was performed for comparing multiple independent groups without normal distribution, the non-parametric Mann-Whitney U test was used as a verification test for the comparison of two independent groups. In addition, the relationship between biochemical parameters used in the follow-up of patients with COVID-19 and the fT3/fT4 ratio was determined through correlation analysis. Since the parametric test condition could not be achieved, relationships between the numerical variables were analyzed using the Spearman Correlation test. The statistical alpha significance level was accepted as $p < 0.05$.

Results

Demographic information and results of the lung tomography belonging to the patient groups participating in the study are presented in Table 1. Among the 114 patients, 64 (56.1%) were males, and 50 (43.9%) were females. We concluded that only isolated low fT3 levels were detected in 39.5% (45/114) of the patients, while 25.4% (29/114) had both isolated low TSH and fT3 levels, 31.6% (36/114) had autoimmune thyroid disease, and 3.5% (4/114) had normal results in the thyroid function tests. When grouping the patients, patients with normal thyroid function tests were not included in any groups as they were quantitatively insufficient. In addition, 102 (89.5%) of 114 patients had ground-glass opacity on lung tomography, while 12 (10.5%) patients had no ground-glass opacity on lung tomography.

The median, interquartile range of the tests belonging to all groups and p-values obtained according to the comparison results of the 3 groups are presented in Table 2. According to the results of the comparison performed within the group, a statistical difference was obtained when fT3/fT4 ratio, TgAb, TPOAb, and fT3 values of Group I and Group II were compared among themselves ($p < 0.01$, $p < 0.01$, $p < 0.01$, $p < 0.01$, respectively); however, no statistical difference was obtained among fT4, TSH, procalcitonin, D-dimer, troponin T, CRP, leukocyte and ferritin levels ($p = 0.220$, $p = 0.488$, $p = 0.079$, $p = 0.642$, $p = 0.347$, $p = 0.229$, $p = 0.168$, $p = 0.197$, respectively). A statistical difference was obtained when the fT3/fT4 ratio, TgAb, TPOAb and fT3, TSH, procalcitonin, CRP and ferritin levels of Group I and Group III were compared among themselves ($p < 0.01$, $p < 0.01$, $p < 0.01$, $p < 0.01$, $p < 0.01$, $p = 0.027$, $p < 0.01$, respectively); however, there was no statistical difference in terms of D-dimer, troponin T and leukocyte values ($p = 0.227$, $p = 0.303$, $p = 0.225$, $p = 0.828$, respectively). A statistically significant difference was obtained when fT3, TSH and ferritin levels of Group II and Group III were compared ($p = 0.047$, $p < 0.01$, $p = 0.018$, respectively); however, no statistically significant difference was obtained when the procalcitonin, D-dimer, troponin T, CRP and leukocyte values were compared ($p = 0.510$, $p = 0.472$, $p = 0.779$, $p = 0.122$,

$p = 0.234$, $p = 0.640$, $p = 0.698$, $p = 0.485$, $p = 0.457$, respectively). The boxplot belonging to the fT3/fT4 ratios is displayed in Figure 1.

According to the correlation results, when the data obtained as a result of the analysis for Group I were compared within themselves, the fT3/fT4 ratio was found to have no statistically significant correlation with TgAb ($r = 0.3$, $p = 0.076$), procalcitonin ($r = -0.014$, $p = 0.935$), D-dimer ($r = 0.058$, $p = 0.735$), troponin T ($r = 0.157$, $p = 0.735$), C-reactive protein ($r = -0.21$, $p = 0.218$), leukocyte ($r = 0.030$, $p = 0.860$), ferritin ($r = -0.279$, $p = 0.099$)

Table 1. Demographic information and lung tomography results of patients with abnormal thyroid function tests

| | Group I (n=36) | | Group II (n=45) | | Group III (n=29) | |
|---|----------------|----------|-----------------|----------|------------------|------------|
| Age (year) (median-IQR) | 56 (46-62) | | 58 (49-62) | | 61 (57-64) | |
| Gender | male | female | male | female | male | female |
| | 18 (50%) | 18 (50%) | 27 (60%) | 18 (40%) | 17 (58.6%) | 12 (41.4%) |
| Ground-glass opacity on lung tomography | Positive | Negative | Positive | Negative | Positive | Negative |
| | 33 (91.6%) | 3 (8.4%) | 42 (93.3%) | 3 (6.7%) | 27 (93.1%) | 2 (6.9%) |

IQR: Inter Quartile Range

Table 2. Median, interquartile range and p values of test belonging to all groups

| Tests | Group I (n=36) | Group II (n=45) | Group III (n=29) | p values |
|------------------------------|-------------------|-------------------|-------------------|----------|
| TgAb (U/L) | 162 (64-278) | 15.5 (13.7-18.6) | 15.8 (14.3-21.6) | 0.001** |
| TPOAb (U/L) | 110 (61-311) | 10.5 (9-16.8) | 10.5 (9.0-12.8) | 0.001** |
| fT3 (pg/mL) | 2 (1.7-2.6) | 1.64 (1.48-1.83) | 1.49 (1.28-1.77) | 0.001** |
| fT4 (ng/dL) | 1.2 (1-1.43) | 1.29(1.18-1.49) | 1.32 (1.10-1.61) | 0.365 |
| fT3/fT4 ratio | 1.74 (1.38-2.53) | 1.24 (1.03-1.48) | 1.06 (0.91-1.34) | 0.001** |
| TSH(µIU/mL) | 0.94 (0.18-2.7) | 0.56 (0.39-1.179) | 0.16 (0.12-0.19) | 0.001** |
| Procalcitonin (ng/mL) | 0.07 (0.03-0.20) | 0.10 (0.05-0.41) | 0.22 (0.07-0.47) | 0.020* |
| D-dimer(ug/mL) | 506 (239-1859) | 674 (229-2831) | 635 (406-2595) | 0.627 |
| TroponinT (ng/mL) | 8 (3.2-11.3) | 8 (4.0-15.9) | 8.20 (5.03-15.8) | 0.443 |
| CRP (mg/dL) | 38.2 (11.9-86.7) | 52.9 (12.7-114.1) | 74.2 (39.6-108.1) | 0.117 |
| leukocyte 10 ⁹ /L | 7.85 (5.85-10.55) | 9.10 (6.85-12.30) | 8.80 (5.00-13.30) | 0.411 |
| Ferritin (ng/mL) | 510 (155-723) | 593 (202-1180) | 1086 (545-1601) | 0.004** |

Abbreviations: TPOAb: Antithyroperoxidase Antibodies, TgAb: Anti tiroglobulin antikor, fT3: Free triiodotironin, fT4: free-tetraiodothyronine, TSH: Thyroid Stimulating Hormone, CRP: C-reactive protein ** <0.01. * <0.05

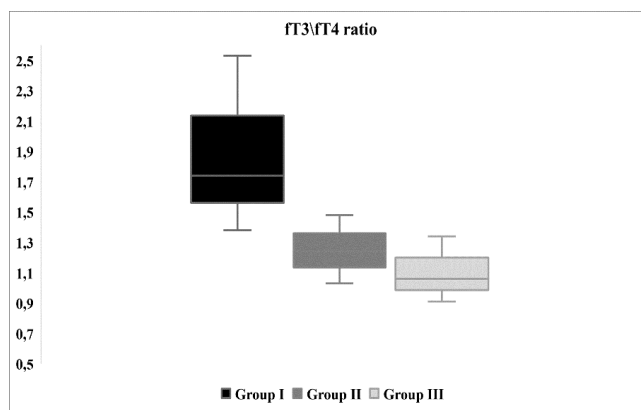


Figure 1. Figure 1. Boxplot belonging to the fT3/fT4 ratios of groups

($p > 0.05$); however, a statistically significant correlation was found with TPOAb ($r = 0.65$, $p = 0.001$) and TSH ($r = 0.397$, $p = 0.010$) ($p < 0.05$). According to the correlation results of Group II, the FT3/FT4 ratio was found to have no statistically significant correlation with TgAb ($r = 0.073$, $p = 0.632$), TPOAb ($r = 0.124$, $p = 0.415$), TSH ($r = 0.213$, $p = 0.159$), procalcitonin ($r = 0.289$), $p = 0.054$), D-dimer ($r = -0.192$, $p = 0.213$), Troponin T ($r = -0.002$, $p = 0.992$), C-reactive protein ($r = 0.087$, $p = 0.576$), Leukocyte ($r = 0.058$, $p = 0.710$), and ferritin ($r = 0.249$, $p = 0.103$) values ($p > 0.05$). Looking at the correlation results of Group III, the FT3/FT4 ratio was found to have no statistically significant correlation with TgAb ($r = -0.146$, $p = 0.451$), TPOAb ($r = -0.237$, $p = 0.216$), TSH ($r = 0.091$, $p = 0.640$), D-dimer ($r = -0.021$, $p = 0.916$), troponin T ($r = -0.049$, $p = 0.805$), C-reactive protein ($r = 0.007$, $p = 0.971$), procalcitonin ($r = 0.330$, $p = 0.080$), leukocyte ($r = 0.185$, $p = 0.337$), ferritin ($r = 0.185$, $p = 0.337$) ($p > 0.05$).

Discussion

This study investigated the change in thyroid hormones in randomly selected patients, who were hospitalized due to COVID-19, and the possible relationship between this change and other biochemical markers used for COVID-19. In the light of the results we obtained, our first notable finding was that 64.9% of these patients had ESS. Our second notable finding was that 35.1% of the patients had autoimmune thyroid disease. It was also noteworthy that the ratio of FT3/T4 was at the lowest value in all groups, especially in Group III, which contained patients with increased severity of thyroid disease. Recent studies have revealed that COVID-19 causes changes in thyroid hormone levels [11-14]. According to data obtained by Lui et al. on 191 patients with COVID-19, they found that it was accompanied by abnormal thyroid function, especially in 25 (13.1%) patients. They reported that 10 of these patients with abnormal thyroid function had isolated low TSH levels, and 10 had isolated low FT3 levels, which they thought were caused by non-thyroid illness syndrome. In addition, they stated in their studies that patients with isolated low FT3 levels had worse outcomes and systemic infection associated with COVID-19 and that isolated low FT3 levels and FT3/ FT4 ratio could be a prognostic marker [15]. In another study, 62 sequential patients, who were treated in the hospital during the COVID-19 pandemic, were included in the study, and the patients were divided into two groups as patients with low serum FT3 levels ($n = 38$ patients) and patients with normal serum FT3 levels ($n = 24$ patients). As a result of their examination, they found that the severity of COVID-19 was higher in the group with low FT3 levels, and that serum FT3 levels were associated with the severity of the disease [16]. In the study conducted by Zou et al., it was found that 41 (27.52%) of 149 patients with COVID-19 had ESS. They reported later in the study that, when patients with COVID-19 who did not have ESS were compared with the patients with ESS, they reported that ESS was significantly associated with inflammation parameters and the severity of the disease in patients with COVID-19 [17].

In the study by Wang et al., which included 84 patients with COVID-19, 91 patients with non-COVID-19 pneumonia, and 807 healthy participants, they found that serum TSH levels were significantly lower in patients with COVID-19 compared to the

other groups. They also reported that this change in patients with COVID-19 may be partly due to ESS [18]. Serum FT4 levels also increase over time as the severity of ESS increases. In our study, the severity of the disease was higher at both central (isolated low TSH) and thyroid hormone (isolated low FT3) levels, especially in Group III patients, the FT4 levels were higher in Group III compared to the serum FT4 levels of Group I and Group II. However, these high serum FT4 levels belonging to Group III were not statistically significant when compared to the other groups. In addition, the statistically significantly higher ferritin levels obtained in Group III compared to other groups were the reflection of the increased acute phase response; therefore, the increase in acute phase response may have caused the suppression of central TSH and 5-deiodinase activity. Our study is a cross-sectional study conducted in a specific region in the Turkish population. The regional and social variability of SARS-CoV-2 strains causes the achievement of different results in previous studies. In addition, regional differences play a large role in immune defense due to genetic features. Accordingly, studies conducted in different populations and different regions become important for understanding the disease mechanisms caused by the SARS-CoV-2 infection in the body. Finally, there is a need for comparative studies, where the changes in different variants of SARS-CoV-2 are examined in patients infected with SARS-CoV-2.

Conclusion

As a result, there was a high prevalence of ESS in patients treated for COVID-19. In addition, we believe that studies with a wider scope of participants are needed for testing the reduction in FT3/FT4 ratio with other biochemical parameters in patients with COVID-19 without known thyroid disease.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

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